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THE ACHIEVEMENTS AND PROSPECTS OF DOMESTIC CHEMOTHERAPY

- USSR -

Following is a translation of an article by Professor A. M. Chernukh and G. Ya. Kivman, Candidate of the Medical Sciences, of the Institute of Pharmacology and Chemotherapy of the Academy of the Medical Sciences USSR (Director -- Professor V. V. Zakusov, Member of the Academy of Medical Sciences USSR), in Sovetskaya meditsina (Soviet Medicine), No 8, Moscow, 1960, pages 39-46.

Chemotherapy occupies one of the leading positions in contemporary medicine. The blossoming of the sciences of antibiotics and synthetic chemotherapeutic drugs has brought about immense results in the treatment of infectious and other diseases in which the infectious agent plays an essential role. Chemotherapy is the most important component part in the numerous measures for lowering the disease rate and for completely liquidating a number of infectious diseases in our country.

The decree of the Central Committee of the CPSU, and the Council of Ministers USSR, "On Measures for the Further Improvement of the Medical Service and Health Protection of the Population of the USSR" has set serious tasks before medical scientists and practicing physicians who to a significant degree are concerned with infectious diseases and malignant neoplasms the liquidation of which depends directly on the development and achievements of chemotherapy.

Research work in the field of chemotherapy is taking different directions in our country. Serious attention is being given to working out general as well as particular problems in chemotherapy. Of essential importance is the discovery of new, effective antibiotics and synthetic drugs to combat various bacterial and fungal infections, virus diseases, and malignant tumors. A great deal of attention is being devoted to creating rational, medicinal kinds of chemotherapeutic drugs. Naturally, this work can be successfully realized only in a thorough study of the action mechanism of chemotherapeutic substances in the microbic cell (virus, malignant tumor) and at the same time in a study of their influence on the macroorganism, especially in the dynamics of the development of the corresponding pathological process.

Thus, on the whole scientific work is being carried out on the chemotherapy of bacterial infections and parasitic diseases, virus infections, and malignant tumors. We shall dwell on the characteristics of several of these.

Chemotherapy of Bacterial Infections

The era of antibiotics in medicine is related mainly to the chemotherapy of bacterial infections. The broader application of chemotherapeutic drugs for the treatment of many infections has brought forward a number of problems of first-degree importance. We are mainly concerned with antibiotics in as much as they occupy the leading place in the therapy of the majority of bacterial infections (in addition to tuberculosis). Synthetic chemotherapeutic drugs have a large part in the treatment of tuberculosis side by side with streptomycin, as is known.

In using antibiotics one must keep in mind their possible side effect and the development of the resistance of microorganisms to them. One may fundamentally consider that there will hardly be found an antibiotic completely devoid of a side effect and which excludes the possibility of microorganisms becoming immune to it. The task of the rational application of antibiotics is to lower as much as possible the number and seriousness of possible complications and to sharply retard if not to prevent the development of resistance to a given drug. A solution to the problems of a rational application of antibiotics at the present time is connected with the necessity of having a sufficient selection of drugs in various medicinal forms.

A number of new drugs have been obtained in our country which have found application in various infections.

In the All-Union Scientific Research Institute for Antibiotics (VNIIA) [Vsesoyuznyy nauchno-issledovatel'skiy institut antibiotikov] a domestic drug has been obtained from a group of polymyxins -- polymyxin M which is differentiated from the foreign polymyxins by its chemical structure (A. S. Khokhlov, and others, 1960). Polymyxin M was subjected to a thorough study in the Department of Chemotherapy of the VNIIA under the supervision of Prof Z. V. Yermol'yeva. Polymyxins have a strong effect on gram-negative bacteria, in particular the cyanomycotic bacillus and in this area have large practical interest.

Antibiotics of the neomycin group have found broad clinical application in surgical infections, infections of the urinary tract, and others: myselin obtained under the supervision of Prof Kh. Kh. Planel'yes in the Institute of Epidemiology and Microbiology imeni N. F. Gamalei of the Academy of Medical Sciences USSR, and colimycin, obtained in the Institute for the Discovery of New Antibiotics of the Academy of Medical Sciences of the USSR, (G. F. Gauze, 1959). Clinical experimentation with a third antibiotic of this group, monomycin, (G. F. Gauze, 1959), also obtained in the Institute for the Discovery of New Antibiotics, is proceeding. Also in the same institute an antibiotic from the ristocetin -- group has been isolated and studied in detail -- actinoidin which will probably find application in the treatment of infections caused by staphylococci, which resist other antibiotics. A drug called fumagillin has been obtained in the VNIIA (R. A. Maksimova and others, 1959) which is effective in treating amoebic dysentery.

Research on active antifungal antibiotics is being widely carried out. Definite achievements have been reached at the present time regarding

these. The industrial production of domestic nystatin has begun, which was obtained in the VNIIA. Discoveries of a second polyene antibiotic -- 26/1 are being studied in the Leningrad Institute of Antibiotics; this antibiotic exceeds nystatin in effectiveness (V. A. Tsyganov and others, 1959). The VNIIA is also conducting a study of albofungin, and antifungal antibiotic of non-polyene structure which also has antibacterial effectiveness (A. S. Khokhlov, G. S. Rozenfeld, 1959).

Side by side with research on new antibiotics a great deal of work is being undertaken in obtaining new penicillins which have a much broader range of effectiveness (M. M. Levitov, 1957) and in the synthesis of salts of penicillin and chlortetracycline with prolonged effectiveness. The latter drug, dibiomycin, (VNIIA), has appeared highly effective in treating trachoma.

The creation of new medicinal forms of antibiotics is of great significance in regard to their rational application as well as to their increase in effectiveness. We have also made definite achievements in this area. Bicillin-1, bicillin-3, and ecmonovocycin (Z. V. Yermol'yeva and others, 1958) obtained in the VNIIA are drugs which have the best prospects for liquidating syphilis and for the prophylaxis of rheumatism; dihydrostreptomycin-paskak and streptomycin-salucide in experiments are effective in regard to streptomycin resistant forms of tuberculosis microbacteria. Tetracyclines for intramuscular administration have appeared highly effective in the treatment of dysentery (Z. V. Yermol'yeva, 1959).

Research in the field of antituberculosis drugs is being undertaken at the present time in three directions (F. V. Shebanov, 1959):

- 1) a study of the properties and a search for the most effective methods of applying drugs already widely used -- streptomycin, phthiyvamide tubazid, and PAS [Para Aminosalicylic Acid];
- 2) the creation of drugs which will supplement streptomycin, phthiyvamide, and PAS in strengthening their effectiveness and in postponing the moment at which resistant forms of tubercular microbacteria emerge;
- 3) the creation of new drugs which will have effect on the resistant forms of tubercular microbacteria.

The majority of new antituberculosis drugs which have been studied in the last few years in the USSR are related to the derivative hydrazides of isonicotinic acid: phthiyvamide, salucide, soluble salucide, and metacide (G. N. Pershin, M. N. Shchukina, and others; All-Union Scientific Research Chemico-Pharmaceutical Institute imeni S. Ordzhonikidze). The antitubercular drug larusan [Russian spelling] is synthesized in the Sverdlovsk Institute of Tuberculosis, and sulfamethin in the Ukrainian Institute of Tuberculosis. Soluble salucide is effective in tubercular meningitis, metacide in tubercular lymphatic nodes, and sulfamethin in tuberculosis of the bone, cold abscess, and fistulas.

The chemical synthesis of the antituberculosis drugs d, l-cyclo-serine and thianide (1314 Th) -- a thiomide of d-ethylisonicotinic acid has been brought about in an original manner recently in the Institute of Pharmacology and Chemotherapy of the Academy of Medical Sciences USSR (N. K. Kochetkov, N. F. Kucherova, R. M. Khomutov, and others). These drugs are being studied in the Department of Experimental Chemotherapy

of the institute (A. M. Chernukh, M. A. Breger, G. Ya. Kivman, and others). In addition to the fact that cycloserine and thianide can supplement streptomycin, phthiivacide, and PAS in strengthening their medicinal effect, they are also effective against a number of medicine resistant forms of tubercular microbacteria.

An original, effective system of combatting tuberculosis which has withstood the test of time has been created in our country. All the improved conditions of labor and life in the USSR, the compulsory tuberculosis vaccination of new-born infants, the wide revaccination of children and adults, and more and more purposeful application of specific methods of treatment in various periods of the development of the disease have played a large role in lowering the disease rate and fatality from tuberculosis and in the prevention of the development of the so-called symptomatic forms. Antibacterial therapy, in addition, has made possible the broader development of the surgical treatment of tuberculosis and has sharply lowered post-operation relapses.

Chemotherapy of Virus Infections

As compared to the large achievements in the chemotherapy of bacterial infections, the chemotherapy of virus diseases may be considered only to be in the beginning of its development. With the exception of infections caused by viruses of the psittacosis group, trachoma, and venereal lymphogranuloma, where the pathogenic agents in a number of characteristics approach rickettsia, achievements in chemotherapy of virus diseases have been very modest (L. A. Zil'ber, 1956). This can be explained by the peculiarities of the physiology of viruses. The absolute parasitism of viruses, which is manifested in the continuous association of their metabolism with the metabolism of the host cells, is the most important obstacle for chemotherapy. Indeed, in order to suppress the multiplication of viruses it is necessary to act on the intracellular processes and this immediately necessitates the solving of many complex problems (Horsfall, 1955; V. L. Ryzhkov, 1957).

The most important of these is that the drug sought for with the specified type of effect must influence the intracellular processes to such a degree that the maximum damage will be done to the virus and practically none to the host. As compared to bacterial infections at the present time it is difficult to visualize a universal anti-virus drug. It is completely apparent that in regard to each virus a compound can be created which does not effect other viruses and also other types of the same virus. This is determined to a great extent by the peculiarities of the metabolism of a given type of virus.

The need for drugs which combat virus infections is immense. It is sufficient to recall influenza in order to thoroughly realize this. Will chemotherapeutic drugs be as effective in virus infections as in bacterial infections? It is impossible to answer this question at the present time in a well-founded manner. Only one thing is clear: the discovery of anti-virus antibiotics and synthetic drugs is made difficult by the reason we

just mentioned. Research on new forms and methods is necessary. Among these cytochemical methods of research must have an essential place.

However there have been already several revealing results in regard to the discovery of antiviral drugs. The chemotherapeutic activity of a number of thiosemicarbazones in experimental influenza infections in white mice was studied in the VNIKhFI Vsesoyuzniy Nauchno-issledovatel'skiy khimikofarmatsevticheskiy institut im. S. Ordzhonikidze - All-Union chemopharmaceutical Research Institute (im. S. Ordzhonikidze), (G. N. Pershin, N. S. Butyrkina, 1954). Cutizone has given definite results among the discovered drugs. It was established that this drug in a maximally bearable dose and doses approaching this in repeated administration protect mice from destruction who have been inoculated with a fatal dose of virus. Cutizone was clinically tested (Z. L. Filippova-Nutrikhina, 1954) with a revealing result. In experiments on chicken embryos inoculated with the type A influenza virus, it was established that an iodide drug and industrial apple pectin prevent the development of influenza infections, however these drugs act less effectively on the type A₁ influenza virus and are not effective against the type B influenza virus. (R. S. Dreyzin, M. I. Karlina, 1954). This work confirms the possibility of creating a drug which is active only in regard to a given type of virus. The influence of various amino acids and other substances on the propagation of the influenza virus and several other viruses has been studied. Definite attention is being given to problems of the methods connected with the experimental study of the action of chemotherapeutic drugs on virus infections and the evaluation of various standards from this point of view.

Antibiotics have been found which have an antiviral activity. A. V. Yermol'yeva, A. K. Shubladze and others (1953) studied the action of a number of antibiotics on an experimental influenza infection: penicillin, the novocaine salts of penicillin, ecmonovocyllin, streptomycin, chlortetracycline, and oxytetracycline. In addition, research was carried out on ekmolin and several other substances. On the basis of experimental, clinical, and epidemiological data, the authors consider ekmolin and ekmolin with penicillin as definitely good prospects in combatting influenza.

An antiviral antibiotic called heliomycin which is active against experimental influenza in white mice was obtained in the Institute for the Discovery of New Antibiotics.

In the Institute of Microbiology of the Academy of Sciences USSR, N. A. Krasil'nikov and his colleagues obtained an antibiotic called violarin [Russian spelling] which suppresses the development of the influenza virus and pox vaccine in experiments on chicken embryos. It has been established in experiments on animals that violarin suppresses the virus of acarid-bite encephalitis.

In the Chair of Microbiology of the Central Institute of the Advanced Training of Physicians the antiviral activity of two antibiotic drugs was studied, the producers of which, isolated from various soils by N. A. Krasil'nikov and A. I. Korenyako, differ from the producer of violarin in several characteristics. In experiments on chicken embryos both drugs proved highly effective and completely suppressed the development of various types of influenza virus under injections of from 10 to 10,000 infectious

doses of the virus. Of course both heliomycin and violarin as well as other similar antibiotics are still far from being used clinically.

Chemotherapy of Malignant Neoplasms

The chemotherapy of malignant neoplasms has a number of general characteristics in common with the chemotherapies of bacterial and virus infections. This idea was broadly and thoroughly laid down in an article by Sh. D. Moshkovskiy published in the Vestnik AMN SSR (Journal of the Academy of Medical Sciences USSR), 1959. The author mentioned many traits of similarity in the nature and mechanisms of chemotherapeutic interference in cancer and infectious diseases. From this arises a number of methodological problems connected with the research and testing of the activity of antiinfectious and antitumor drugs. This, naturally, does not mean that the principal differences between infectious and tumor processes can be ignored in any degree whatsoever. A tumor cell is a sharply altered, derivative normal cell of an organism whereas a microbe or virus is not genetically connected with the tissues of an organism. The discovery and study of antitumor substances is linked with additional difficulties which consist in a noncorrespondence of many experimental tumors in animals to human tumors. In the laboratory directed by L. F. Larionov (Institute of Experimental Pathology and Cancer Therapy of the Academy of Medical Science USSR), experiments are being carried out on the heterotransplantation of human tumors to animals and their cultivation in vitro with the purpose of obtaining data on the sensitivity of various human tumors to antitumor drugs. While it is still too early to speak of the practical results of this work (and other work of a similar nature), the direction this research is taking indicates very good prospects.

It is possible to say that for the past few years changes in the search for synthetic and natural antitumoral substances were planned. The domestic experimental and clinical oncology is being directed at the present time toward a selection of active compounds which will make possible research aimed at discovering antitumor drugs. From this point of view the antitumor drugs of the alkylating metabolite type are of special interest (L. F. Larionov 1959). Simple compounds of this series consist of the cytotoxic, chemical group (with alkylating action) which are added to the metabolite -- participator in the nuclein or proteometabolism which takes place very intensively in tumors. According to the supposition of L. F. Larionov, the metabolite can be not only the carrier but also the conductor of cytotoxic groups in tumors. Dopan, sarkolysin and other compounds which are distinguished as carriers were created on this basis. According to clinical data of N. N. Blokhina (1956, 1958) these drugs have a different range of effect on tumors. Thus, one of the principle schemes of antitumor drugs was created, however, this is not by far the only one possible.

Subsequently more complex compounds were created in which the carrier of the cytotoxic group consists of two parts which are connected with the peptide, amide, or ester bond. These bonds can be subjected to a fermentive cleavage in the organism. Such compounds are related to the complex alkylating metabolites. More than 30 such drugs have been studied

in the Institute of Experimental Pathology and Cancer Therapy. The majority of them have a significant antitumor effect in experimentation with little toxicity.

In considering what has been said above, it is impossible to predict with sufficient reliability which one of these drugs can prove effective with particular tumors. The answer to this question will have to be given in the near future.

Thus the problem of creating antitumor chemical compounds is now in the stage of guided synthesis. The period of the empirical testing of masses of the most diverse substances as the only one possible is now past. Furthermore, chemical compounds obtained for other purposes (frequently quite far removed from the tasks of tumor therapy) in a number of cases can be tested for antitumor activity. At the present time this approach is neither the main one nor the only one. The further study of the biochemistry of tumoral cells in comparison to normal cells will make it all the more possible to go over exclusively to a controlled synthesis of antitumoral drugs.

Antibiotics are beginning to occupy a serious place in solving the problems of the therapy of malignant neoplasms side by side with the synthetic antitumor drugs. If we consider that the characteristic properties of a number of antibiotics is their selective activity on biochemical processes, we have all the reason to hope that those drugs will be discovered which will suppress the growth of cancer cells while remaining practically harmless (or of little toxicity) to normal cells of the organism. Naturally in these cases there is always the danger of obtaining an antibiotic with a less than permissible gap between the therapeutic and toxic dose, but this, as is known, is by far not excluded either in research on antibacterial antibiotics or, as unfortunately happens quite frequently in research on antiviral drugs. This to a significant degree is determined by the greater or lesser differences in the metabolic processes of the substratum on which the activity of the chemotherapeutic drug must be directed in comparison to the metabolism of the cells of the host and the accessibility of the substratum to the effect of the drug (problems of permeability and the inactivation of the drug in the organism, etc.) and other factors. Naturally, antibiotics in this regard do not principally differ from synthetic chemotherapeutic drugs. More than this, the deciphering of the structure of anticancer antibiotics can render essential aid to research in synthetic antitumor drugs. Research in anticancer antibiotics, which we have undertaken with special intensiveness in the last few years, has led to revealing results.

An antitumoral antibiotic called actinoxanthin has been obtained in the All-Union Scientific Research Institute of Antibiotics; at the present time is undergoing clinical testing. An anticancer antibiotic 6270 has been obtained from a culture of *Actinomyces* in the Institute for the Discovery of New Antibiotics; an antitumoral antibiotic called mutomycin has been isolated in the same institute. In the Institute of Microbiology and Epidemiology imeni N. F. Gamalei an antitumor antibiotic called auranthiin has been obtained from a culture of *Actinomyces*; this antibiotic is close to actinomycin C in chemical structure. Auranthiin is undergoing

clinical testing at the present time. Work on the use of an anticancer drug from schizotrypan is being conducted in the State Institute for the Control of Medical and Biological Drugs imeni L. A. Tarasevich. An anti-tumor antibiotic neocid has been obtained and is being clinically applied in the Khar'kov Institute of Vaccines and Serums imeni I. I. Mechnikov.

It is necessary to mention, however, that the enumerated drugs are still far from having all the properties necessary for medicinal anti-tumor drugs.

We are undertaking the research and study of antitumoral antibiotics on a large front. We have all the reasons to think that this will bring definite practical results in combatting such heavy suffering to man as is caused by malignant neoplasms.

Among the problems of chemotherapy the study of the general mechanisms of the fate of chemotherapeutic drugs in the organism is of essential importance (absorption, distribution, combining with tissues, etc.) and the clarification of the peculiarities of their influence on the reactions of the macroorganism.

It is known that in the process of convalescence of an infected sick person the termination of the disease is resolved by the liquidation of the pathogenic agent or by a significant raising of the sensitivity threshold of the macroorganism to the agent. In the final result the condition of the defensive and compensatory reactions of the macroorganism decides the matter. Several scientific institutions of the country (The Institute of Pharmacology and Chemotherapy, the Institute of Microbiology and Epidemiology imeni N. F. Gamalei, the Leningrad Institute of Antibiotics, and others) have been occupied over a number of years with the study of the mechanisms referred to. It has been shown that in the process of the chemotherapy of infectious diseases of neural and endocrine regulation, the immunity reaction, and the condition of the endothelial-macrophagial system are altered. Here the functional condition of the macroorganism is very important.

In connection with the presence of a negative, secondary influence on the macroorganism of a number of antibiotics and synthetic chemotherapeutic drugs, their combined application with pharmacological drugs, for example with antihistamines and antiallergy compounds, and others has acquired special significance (besides the rational application of these drugs).

The further combined work of chemotherapists and chemists in clarifying the relation between the chemical structure of various types of compounds and their biological effect is highly important in the further successful development of domestic chemotherapy especially in working out the general principles of a controlled synthesis of new chemotherapeutic drugs. In this work biochemical and physico-chemical methods of research must be widely utilized.

The fruitfulness of such a collaboration is shown in many foreign and domestic research projects. In the Institute of Pharmacology and Chemotherapy this led to the discovery of the effect of cycloserine on the process of transaminization (Ye. D. Vyshepan and others, 1959).

It is impossible to include in one article all the divisions of chemotherapy and sciences which at the present time have immense importance for the practice of public health. We have dwelt only on the main, foremost problems for the sake of attracting the attention of the larger groups of scientific workers and practicing physicians to the necessity of a significant expansion in general and specific chemotherapy.

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